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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,559	10/15/2004	Tim Jones	MER-133	4176

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EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,559	JONES ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-21 and 24-31* is/are pending in the application.

4a) Of the above claim(s) *19 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20 and 24-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received April 5, 2006 are acknowledged.
Claims 1-17, 22, and 23 have been canceled.
Claims 18-21 and 24 have been amended.
Claims 26-31 have been added.
Claims 18-21, and 24-31 are pending in the instant application.
Claims 19 and 21 stand withdrawn from consideration as being drawn to a nonelected species. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the Office Action mailed September 20, 2005.

Claims 18, 20 and 24-31 are under examination as the read on FVIII polypeptides comprising the epitope of residues 817-831 of SEQ ID NO:73 with the specific point mutation V823A. This specific mutation does not appear to be disclosed in the prior art, and as such the search has been extended beyond the elected species.

Information Disclosure Statement

2. Applicant's IDS received April 5, 2006 is acknowledged and has been considered.

Priority

3. As discussed in the prior office action, the instant application claims foreign priority to two European Patent Office documents, 02008712.8 filed 4/18/2002, and 03006554.4 filed 3/24/2003. All pending claims currently recite the limitation of SEQ ID NO:73, a full length FVIII polypeptide. The priority documents do not disclose this sequence and therefore the priority date given to the instant claims for their examination in relation to the prior art is the filing date of the instant application, namely April 17, 2003.

Drawings

4. Applicant's replacement drawings received as part of the preliminary amendment filed on October 15, 2004 are acknowledged, and the objection of record is withdrawn because Figure 1 as amended identifies each sequence via a SEQ ID number in accordance with 37 CFR 1.821-1.825.

Specification

5. The amendment filed April 5, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant's alteration of the paragraph beginning at page 41, line 32. This paragraph in the original specification indicates that amino acids A, C, D, E, K, N, P, Q, R, S, and T are anchors for peptide binding to MHC class II molecules. Applicant's amendment reword this part of the specification to state that amino acids A, C, D, E, K, N, P, Q, R, S, and T do not have the potential to serve as anchors for binding to MHC class II molecules, and applicant argues that these changes have been made to achieve consistency with language used on line 22 of page 44 of the original specification. It is noted that the specification is not internally consistent, but as is discussed more fully later in this office action, Rammensee et al. teach that these amino acids do serve as anchors. Since the art teaches that these amino acids are anchors for MHC class II binding, altering the specification to state that they are not anchors is new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not provide antecedent basis for the phrase "biological specificity". This phrase was present in claim 1 as originally filed and as such it does not constitute new matter.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. The rejection of claims 1-5, 8, 9, 11, 17, 18, 20, 24, and 25 under 35 U.S.C. 101 for claiming non-statutory subject matter has been obviated by applicant's amendments received April 5, 2006 that either canceled claims or amended claims such that the recited polypeptide is isolated, thus clearly indicating the hand of man in the claimed subject matter.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The rejection of claims 8, 9, and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been obviated by applicant's cancellation of claims 8 and 9 and the amendment to claim 20 received April 5, 2006 that clarifies the number of mutations made at position 823 of SEQ ID NO:73.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 18, 20, and 24-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection of record states that:

Applicant has claimed FVIII molecules that have a different sequence from wild type human FVIII, with the sequence differences encompassing the removal of a T cell epitope. It is disclosed that an epitope is removed when in its mutated form the epitope sequence can no longer be bound by MHC class II molecules. Applicant discloses numerous peptides thought to be bound by MHC class II molecules that can evoke a proliferative T cell response in Tables 1 and 2 of the instant specification, and has an example wherein single amino acid substitutions at position 823 of FVIII are tested for their ability to be efficiently expressed and for biological activity in a clotting assay (see particularly from line 30 of page 41 to line 2 of page 43). Applicant discloses that the valine (V) at position 823 is a potential anchor residue important for binding to MHC class II molecules, and discloses that the amino acids A, C, D, E, K, N, P, Q, R, S, and T can also serve as potential primary anchor residues (see particularly lines 34 and 35 of page 41 of the instant specification). Residue 823 was chosen based on computer simulations of MHC class II binding, but no experimental data appears to be provided to confirm that V823 is an anchor residue important for binding to MHC class II molecules and that substitutions of this amino acid residue actually inhibit MHC class II binding or reduce the proliferative response elicited from FVIII-specific T cell clones (see particularly the paragraph that spans pages 26 and 27, and Figure 9).

Applicant has claimed modified FVIII sequences with reduced immunogenicity, some of which incorporate specific substitution mutations at position 823 of FVIII. These recited substitution mutations include the replacement of V823 with A, D, E, G, H, N, P, S, and T. It is particularly noteworthy that the specification teaches that amino acid residues including A, D, E, N, P, S, and T can all act as primary anchor residues (see lines 34 and 35 of page 41). As such it appears that replacement of V with any one of these residues results in exchanging one anchor residue for another. Based on the teachings of the specification concerning the identity of amino acids that can serve as anchors, one would expect that FVIII molecules containing A, D, E, N, P, S, or T in place of V at position 823 would still bind MHC class II molecules and thus still be T cell epitopes.

All of the epitopes in FVIII identified by applicant, as well as the putative anchor residues within these epitopes that are necessary for binding to MHC class II molecules, are disclosed by applicant as having been identified by a computer program. It is known that different class II molecules bind different amino acid sequences and that there may be multiple binding sequences in FVIII for one class II molecule and none for another (White et al., Haematologica, 2000, 85:113-116, see entire document). Predicting the binding of a peptide to an MHC class II molecule is a difficult process complicated by the size heterogeneity peptides bound by MHC class II ligands, and predictions are far from perfect (Nielsen et al., Bioiformatics, 2004, 20:1388-1397, see entire document, particularly the first sentence of the paragraph that spans the left and right columns of page 1396). Indeed, many studies have predicted peptides that cannot be observed to bind to MHC class II molecules when experimentally tested (Cocholvius et al., J. Immunol., 2000, 165:4731-4741, see entire document, particularly Table I, Figure 3, and the paragraph that spans the left and right columns of page 4738). As such, identification of MHC class II binding epitopes can be greatly aided by predictive computer programs, but the current state of such predictions is that they still require laboratory experiments to verify the accuracy of the prediction (Cocholvius et al., see particularly the first full paragraph of the left column of page 4739 and the first sentence of the last paragraph in the right column of page 4739). As such, it appears that the determination of MHC class II binding cannot be predicted based only upon *in silico* methodologies.

Further, substitutions designed to eliminate binding of an epitope to one particular MHC class II molecule may end up creating a new epitope that is capable of binding to some other MHC class II molecule (Jones et al., J. Thromb. Haemost. 2005, 3:991-1000, see entire document, particularly the last 3 sentences of the paragraph that spans pages 998 and 999). As such, mutating the sequence of FVIII may actually result in a molecule that has increased immunogenicity as compared to the parent molecule. Even if such mutations do not generate a new T cell epitope, they may introduce a new B cell epitope (Jones et al., see particularly the second complete sentence of the left column of page 999). B cell epitopes can result in the production of inhibitory antibodies that bind FVIII, and such unwanted antibody responses are a major problem in the treatment of many hemophilia patients (White et al., see entire document, particularly the abstract). Additionally, many deleterious substitution mutations in FVIII have been identified in hemophilia patients, some of which are located in positions indicated by applicant as desirable amino acids to mutate, such as positions 198 and 201 of SEQ ID NO:73 (see printouts of the FVIII point mutation database listing downloaded from the HAMSTeRS database at europium.csc.mrc.ac.uk/WebPages/Main/main.htm), and it is known that the phenotypic results of a mutation in FVIII, such as alteration of biological activities, are correlated more with the position of the amino acid change within the 3D structure rather than with the identity of the actual alteration itself (Cutler et al., Human Mutation, 2002, 19:274-278, see entire document,

particularly the abstract). Therefore, it does not appear likely that many of the positions recited for substitution mutagenesis by applicant such as those in claims 5 and 18 would permit modified FVIII molecules to have the same specificity and activity when used *in vivo*.

Therefore, based upon the fact that different class II molecules bind different peptide sequences and that the particular class II alleles bound by the epitopes of the instant invention are not recited, the fact that prediction of epitopes that bind to MHC class II molecules with computer programs is not predictable since putative epitopes must still be validated experimentally, the fact that the breadth of applicant's claims reads on mutations to FVIII in general as well as in specific locations, the apparent lack of experimental binding data to verify that V823 (and many positions recited in claims 5 and 18 for example) is an MHC class II anchor residue and that substitutions of this amino acid decrease binding, the fact that mutations made in an attempt to decrease immunogenicity may lead to the introduction of new epitopes that are capable of binding MHC class II molecules, the fact that mutations may introduce new B cell epitopes and thus increase overall immunogenicity or otherwise alter the biological activity and specificity of FVIII when used *in vivo* due to alteration of the 3D structure of FVIII, a skilled artisan would be unable to make and use applicant's claimed invention without conducting additional research.

Applicant's arguments received April 5, 2006 are not convincing. Applicant argues that the cancellation of many broad claims has narrowed the scope of the invention to allowable subject matter. Applicant further argues that lines 34-35 of page 41 do not teach that amino acids A, C, D, E, K, N, P, Q, R, S, and T serve as primary anchor residues for binding to MHC class II molecules, and has amended this passage to be in accord with the unambiguous passage of line 22 of page 40 of the specification which teaches that said amino acids are not MHC class II primary anchor residues. Applicant further argues that the claims do not require a reduction in binding to MHC class II molecules but rather only require reduced immunogenicity as can be assayed by T cell proliferation assays, and that individual allotypes need not be considered because the in silico methods used by applicant considered the binding properties of roughly 76 human HLA-DR allotypes.

These arguments are not convincing because a skilled artisan would know that the amino acid residues discussed above do serve as primary anchors for bind MHC class II molecules. For example, Rammensee et al. teach that A is an anchor residue for MHC class II molecules including HLA-DRB1*0101 and DPA1*0102/DPB1*0201, while Q, S, T, and K serve as anchors for HLA-DRB1*0402(Dr4Dw10) and other human class II molecules (Immunogenetics, 1995, 41:178-228, see entire document, particularly Table 6 beginning on page 211). As such these residues are anchors and the identities of the HLA molecules expressed in a person are of critical importance in determining immunogenicity. Applicant's arguments concerning the importance of

proliferation rather than MHC binding per se are unconvincing because if the antigen presenting cells used in the T cell proliferation assay lack the appropriate MHC molecules to present an epitope of FVIII that has been modified at a position of FVIII as recited in the claims no proliferation will result even though such a mutation might induce a potent proliferative response in another MHC background. Further, the claims do not recite that immunogenicity is defined via a T cell proliferation. Additionally, the argument that the disclosed in silico methods sufficiently address binding concerns are not persuasive because as discussed above the computer-identified non-anchor residues do serve as anchors in some human DR molecules, and because the class II molecules DP and DQ exist in humans, the binding properties of which have not been considered.

The identity the amino acid used to replace the wild-type residue of FVIII at a given position is not a limitation recited in all claims. The rejection of record states:

> Additionally, many deleterious substitution mutations in FVIII have been identified in hemophilia patients, some of which are located in positions indicated by applicant as desirable amino acids to mutate, such as positions 198 and 201 of SEQ ID NO:73 (see printouts of the FVIII point mutation database listing downloaded from the HAMSTeRS database at europium.csc.mrc.ac.uk/WebPages/Main/main.htm), and it is known that the phenotypic results of a mutation in FVIII, such as alteration of biological activities, are correlated more with the position of the amino acid change within the 3D structure rather than with the identity of the actual alteration itself (Cutler et al., Human Mutation, 2002, 19:274-278, see entire document, particularly the abstract).

The specification also teaches that not all residues when used to replace a particular position in FVIII yield a polypeptide that retains biological activity (see particularly lines 4-12 of page 40). As such, it is clear that substitution mutations at many of the positions recited by applicant, especially without a recitation of what the substituted amino is to be, yields a polypeptides that lacks the recited functional properties. Applicant has not addressed this aspect of the rejection of record.

Therefore, based upon the breadth of the claimed invention, the fact that immunogenicity as measured by T cell proliferative activity is not meaningful outside the context of a defined MHC genetic background, the fact that immunogenicity is not recited as being measured by T cell proliferative capacity, the fact that residues taught by the instant application as not being MHC class II anchor residues are known anchor residues for some human HLA molecules, the fact that the art teaches that mutations to

FVIII at some of the recited positions are deleterious, and the teachings of the specification that not all amino acids can be substituted at the recited positions commensurate with the retention of recited functional properties, a skilled artisan would be unable to make and use applicant's claimed invention without conducting additional undue research.

12. Claims 18, 20, and 24-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The rejection of record states that:

> Applicant's claims broadly read on all FVIII molecules that contain an amino acid sequence that is different from wild type FVIII such that the binding of a T cell epitope to an MHC class II molecule is reduced or eliminated. Applicant has also recited some specific locations within FVIII that are thought to be suitable for substitution mutagenesis to decrease immunogenicity and MHC class II binding. To support the claimed genus of modified FVIII molecules, applicant has disclosed the generation of substitution mutants for the epitope comprising amino acid V823. These molecules were tested for expression and clotting activity but were not tested for MHC class II binding or for the ability to induce a proliferative T cell response (see particularly Figure 7). Applicant discloses that a computer program is to be used to identify MHC class II binding epitopes and to identify substitution mutations that reduce binding (see particularly the paragraph that spans pages 26 and 27 and Figure 9). It does not appear that data has been provided that verifies the accuracy of the computer predictions with regard to MHC class II binding.
>
> Many point mutations in FVIII are known, most of which are deleterious for biological activity, presumably due to disturbances in the 3D structure of the FVIII molecule (see printouts of the FVIII point mutation database listing downloaded from the HAMSTeRS database at europium.csc.mrc.ac.uk/WebPages/Main/main.htm and Cutler et al., Human Mutation, 2002, 19:274-278, see entire document, particularly the abstract). It is also known that computer algorithms used to predict binding to MHC class II molecules are far from accurate, and that experiments must be performed to verify the ability of any putative epitope to be bound by MHC class II molecules and recognized by T cells (Nielsen et al., Bioiformatics, 2004, 20:1388-1397, see entire document, particularly the first sentence of the paragraph that spans the left and right columns of page 1396 and Cocholvius et al., J. Immunol., 2000, 165:4731-4741, see entire document, particularly Table I, Figure 3, the paragraph that spans the left and right columns of page 4738, the first full paragraph of the left column of page 4739 and the first sentence of the last paragraph in the right column of page 4739). It is also known that substitution mutations in FVIII can increase the immunogenicity of the molecule, either through the introduction of new MHC class II binding epitopes that can be recognized by T cells or by the introduction of novel B cell epitopes that elicit an antibody response (Jones et al., J. Thromb. Haemost. 2005, 3:991-1000, see entire document, particularly the top of the left column of page 999).
>
> Given all of the above, including the apparent lack of data verifying that the disclosed mutations to FVIII at all positions result in both reduced immunogenicity and in maintenance of biological activity of FVIII, a skilled artisan would reasonably conclude that applicant was not in possession of the claimed genus of modified FVIII molecules that retain the biological activity of FVIII yet are less immunogenic due to substitution mutations that reduce MHC class II binding of T cell epitopes. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant has argued that the cancellation of claims has reduced the breadth of the claims such that the remaining claims have written description, and that the disclosed ex vivo testing in a T cell proliferation assays of modified FVIII molecules comprising the mutation recited in claims 20 and 29 demonstrates a correlation between a recited structure and function.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Proliferation of T cells is not a function recited in all claims. All pending claim do recite the functional property of having the same biological specificity as wild type FVIII when used in vivo, but the specification does not define what it means to have the same biological specificity as wild-type FVIII. As such, there is no correlation disclosed in the specification between this functional property and the recited structural limitations. Therefore a skilled artisan would reasonably conclude that applicant was not in possession of the claimed subject matter.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. The rejection of claims 1 and 11 under 35 U.S.C. 102(b) as being anticipated by Tiarks et al. (Scand J Immunol, 1992, 36:653-660, see entire document) has been withdrawn in light of applicant's amendments received April 5, 2006. These amendments have canceled claims 1 and 11, and Tiarks et al. do not teach the limitations recited in the pending claims concerning the position of the mutations within FVIII.

15. The rejection of claims 2-4, 9, 17, and 24 under 35 U.S.C. 102(a) as being anticipated by Jacquemin et al. (Blood, 2003, 101:1351-1358, see entire document, available online October 17, 2002) has been withdrawn in light of applicant's amendments received April 5, 2006. These amendments have canceled claims 2-4, 9, and 17 and have changed the dependency of claim 24. Claim 24 now refers to claim 18, and the specific positions at which a FVIII is mutated in claim 18 or in any other pending claim are not taught by Jacquemin et al.

16. The rejection of claims 2-4, 9, 17, and 24 under 35 U.S.C. 102(a and e) as being anticipated by WO 02/098454 A2 (see entire document) has been withdrawn in light of applicant's amendments received April 5, 2006. These amendments have canceled claims 2-4, 9, and 17 and have changed the dependency of claim 24. Claim 24 now refers to claim 18, and the specific positions at which a FVIII is mutated in claim 18 or any other pending claim are not taught by WO 02/098454 A2.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. The rejection of claims 1-4, 9, 17, and 24 under 35 U.S.C. 103(a) as being unpatentable over Tiarks et al. (Scand J Immunol, 1992, 36:653-660, see entire document) in view of Laub et al. (WO 96/02572A2, see entire document) as evidenced by the English language equivalent US Patent No. 6,866,848, see entire document) has been withdrawn in light of applicant's amendments received April 5, 2006. These amendments have canceled claims 1-4, 9, and 17 and have changed the dependency of claim 24. Claim 24 now refers to claim 18, and neither Tiarks et al. nor Laub et al. teach or provide direction toward mutating FVIII ant the positions recited in all currently pending claims.

The following are new grounds of rejection.

19. Claims 18, 20, and 24-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, independent claim 18 recites a modified human FVIII molecule that is substantially non-immunogenic and that has essentially the same biological specificity as wild-type human FVIII. The metes and bound of this claim and its dependent claims

are uncertain because the specification does not define "substantially non-immunogenic". Does this mean not all individuals comprise T cells that recognize the modified FVIII, that only some percentage of the T cell population of a single individual recognizes the modified FVIII, or that when recognized by T cells the resulting proliferative and cytokine responses are attenuated as compared to wild-type FVIII? What level of diminution or attenuation comprises substantially? Is it 90%, 50%, 10% or something else entirely?

The claims are also indefinite due to the recitation of biological specificity. The specification functionally defines FVIII as a protein that is capable of correcting the coagulation defect in plasma derived from patients affected by hemophilia A (see particularly lines 26-27 of page 5 of the specification) but this is not the same thing as biological specificity, and the specification does not define what is meant by the term "biological specificity". Is the biological specificity the ability to bind other components of the coagulation cascade such as von Willebrand factor, the ability to act as a cofactor for factor IXa in the conversion of factor X to factor Xa, the ability of FVIII to be activated by thrombin, or something entirely different, such as the ability to act as an antigen in the generation of antibodies?

Note that none of the dependent claims further define biological specificity or the property of being substantially non-immunogenic, and as such all pending claims are indefinite.

Additionally, independent claims 18 and 27 recite modified FVIII polypeptides having the amino acid sequence of SEQ ID NO:73 and including substitution mutations at specified positions. If a polypeptide has a recited sequence, the polypeptide is limited to that exact sequence. It is not logical that a polypeptide that has an exact sequence can also comprise mutations, since the presence of said mutations would mean that the polypeptide no longer has the exact recited sequence. As such, the metes and bounds of the claim are unclear. Is applicant attempting to claim modified human Factor VIII molecules that differ from SEQ ID NO:73 at specific positions, or is applicant attempting to claim something else?

Claims 18, 24, 26, 27, 28 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwaab et al. (Brit. J. Haematology, 1995, 91:458-464, see entire document).

Schwaab et al. teach human FVIII polypeptides isolated from hemophilia patients that were tested for their activity and for the presence of mutations (see entire document, particularly the abstract and Table III). The FVIII polypeptide isolated from patient HP37 comprises a mutation from the wild-type FVIII sequence at position 412, a position recited in independent claim 18 and dependent claim 28. The mutant FVIII of patient HP37 is substantially non-immunogenic as evidenced by the fact that no inhibitory antibodies that bind FVIII were detected in his serum as is indicated in Table III. The mutant FVIII polypeptide was present in pharmaceutical compositions comprising buffers for use in the disclosed clotting and ELISA assays (see particularly the Materials and Methods subsection *Patients* on page 458).

Schwaab et al. did not conduct T cell proliferation assays comprising their mutant FVIII polypeptides. However, the USPTO does not have the capability of testing the functional properties of prior art molecules, and given that the structure of the polypeptide recited in independent claim 18 is anticipated by the structure of the polypeptide disclosed by Schwaab et al., the polypeptide disclosed by Schwaab et al. also comprises the recited functional properties.

It is noted that claim 27 and its dependent claims recite that the mutant position in FVIII is identified by a computer modeling technique. Applicant is reminded that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). The structure of the claimed modified human FVIII polypeptide is not altered by the recitation of a computer modeling step, and as such the polypeptide identified by Schwaab et al. anticipates the claimed invention.

20. No claims are allowable.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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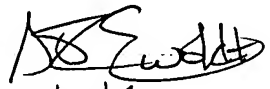
June 15, 2006



6/21/06

G.R. EWOLDT, PH.D.
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